REMARKS

Interview Summary #1: Applicants' agent thanks the Examiner for the telephone interview graciously provided on October 7, 2010, in which all claims were discussed. The MPEP suggests that, to be complete, an interview summary—even when one is already received from the examiner--must address the following issues. Applicants' summary follows each category.

(A) a brief description of the nature of any exhibit shown or any demonstration conducted;-------None

(B) identification of the claims discussed;------64-75

(C) identification of specific prior art discussed; ------- Asano

(D) identification of the principal proposed amendments of a substantive nature discussed, unless they are already described on the Interview Summary form completed by the examiner; ------- None

(E) the general thrust of the principal arguments of the applicant and the examiner should also be identified; ------- Applicants' agent contended that the 103 rejection over Asano is not germane to claims in which specific compound stereochemistry is included.

(F) a general indication of any other pertinent matters discussed;------None

(G) if appropriate, the general results or outcome of the interview; -----Examiner agreed that the 103 rejection should be withdrawn for all claims with stereochemistry specified.

Interview Summary #2: Applicants' agent thanks the Examiner for the telephone interview graciously provided on October 15, 2010, in which all claims were discussed. The MPEP suggests that, to be complete, an interview summary—even when one is already received from the examiner--must address the following issues. Applicants' summary follows each category.

(A) a brief description of the nature of any exhibit shown or any demonstration conducted;-------None

(B) identification of the claims discussed;------64-75

(C) identification of specific prior art discussed; ------- None

(D) identification of the principal proposed amendments of a substantive nature discussed, unless they are already described on the Interview Summary form completed by the examiner; ------- Applicants' agent asked if a disease or condition to be treated can be added to the claims if it has support in the application, and a reference can be provided indicating that the experimental procedure performed in the application for that disease or condition is known to be an accepted model of that disease or condition

(E) the general thrust of the principal arguments of the applicant and the examiner should also be identified; ------- None

(F) a general indication of any other pertinent matters discussed;------None

(G) if appropriate, the general results or outcome of the interview; -----Examiner agreed that the evidence provided in (D) *supra* should be sufficient to allow the disease or condition in the claims.

Office Action Response:

Claims 1-44 were presented at the time of entry into the national phase under 35 USC 371. By preliminary amendment accompanying the filing, claims 1-44 were canceled and new claims 45-63 were entered. In response to a Restriction Requirement, claims 45-62 were elected and claim 63 was withdrawn from consideration. In response to an election of species for examination, Applicants elected the species of claim 46 in which R is hydrogen for the treatment of bacterial infection. This species was read upon by claims 45-48, 54-56 and 58-62. In the previous communication, claim 45 was amended. In the interest of moving this application toward allowance, claim 63 has been canceled; however, Applicants reserve the right to pursue this claim, and any other canceled claims, in a divisional application. In this communication, claims 64-75 are canceled and new claims 76-89 are added. Therefore, the claims currently pending are 76-89. No new matter has been added, and support for all amendments can be found in the specification. The table below is added to assist the Examiner in following the train of current amendments:

Old claim number	New claim number
64	76, 87
65	77
66	78
67	79
68	80
69	81
70	82
71	83
72	84
73	85
74	86
75	88, 89

Addition of Melanoma to Claims: Applicants thank the Examiner for her advice in the telephone call of October 15, 2010, in which she indicated that if there was support in the specification for a particular disease and Applicants could provide a reference showing that the particular model was relevant to treatment, that the disease could be allowed in the claim. Applicants have added melanoma as a disease or condition to be treated. Support for this assertion can be found in Example 7 of the specification as originally filed; this example shows efficacy data against B16-F10 tumor cells, which are melanoma cells. Additional support can be found in the description at page 28, lines 34 et seq.:

> *The invention finds application in the treatment of proliferative disorders, including various cancers and cancer metastasis. For example, the pyrrolizidine compounds of the invention may find particular application in the treatment of leukemias, lymphomas, melanomas ...*

The Overwijk journal article included with this submission as Appendix A (Overwijk WW and Restifo NP, "B16 as a Mouse Model for Human Melanoma", *Curr Protoc Immunol.* 2001 May; CHAPTER: Unit–20.1) demonstrates that B16 cells are indeed a well-known model for melanoma in humans. Explicit support can be found in the Background at pages 24-25, in Table 20.1.2 and in the footnote to Table 20.1.2 on page 32:

> *In conclusion, B16 melanoma is a reasonable model for human melanoma. If anything, its rapid growth, low MHC Class I expression, and its unresponsiveness to adoptive CTL treatment of subcutaneous disease compare unfavorably with most human melanomas and suggest treatment of B16 is a* ***rigorous*** *test for immunotherapy of murine cancer.* [Emphasis added.]

Applicants argue that the above evidence clearly supports the proper addition of "melanoma" to new claims 76 and 87-89.

Rejection of claims under 35 U.S.C § 112

Claims 64-75 are rejected under section 112, first paragraph, as being indefinite related to the term "derivative". Applicants respectfully disagree, as support for the definition of "pharmaceutically acceptable derivative" can be found in the application as filed on page 20, lines 15-28. Lines 19-20 specifically state, "Preferred derivatives are those obtained (or

obtainable) by alkylation, esterification or **acylation** of the parent pyrrolizidine compounds of the invention" (emphasis added).

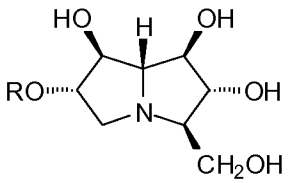
In order to advance prosecution, however, new claims 76 (corresponding to old claim 64) and 87-89 have been limited to more clearly delineate what is to be claimed by defining "acyl derivative" as (C_1-C_4) acyl. Support for this amendment can be found in originally filed claim 13 (most recently, claim 68; currently claim 80): "...wherein the acyl derivative is an alkanoyl derivative selected from acetyl, propanoyl and butanoyl." Further, page 14 of the originally filed application discloses 6-*O*-butanoylcasuarine. The person of skill will recognize that any of the hydroxyl groups at the other positions may also be acylated.

Old claim 71 (new claim 83) is separately rejected under 112 for the same reason. Claim 83 is dependent on new claim 76. With the amendment of claim 76, Applicants respectfully request the withdrawal of the 112 rejection.

Rejection of claims under 35 U.S.C § 103(a)

Claims 64-75 are rejected under section 103(a) as being obvious over Asano and Immune-strategy, both previously cited. Applicants respectfully disagree with this rejection. As discussed in the telephone call of October 7, 2010 (summarized above), the Examiner has withdrawn the 103 rejection for all claims with specified stereochemistry. Therefore, claims 64 and 72-75 (now 76 and 84-87, and new claims 88-89) are the only claims still subject to the 103 rejection. Applicants believe this rejection is improper because the Examiner has not established a *prima facie* case for obviousness. However, in order to advance prosecution, new claim 76 (corresponding to old claim 64) and new claim 89 have been amended to specify the stereochemistry of the compounds to be claimed. None of these compounds possess the stereochemistry of the Asano compounds, nor do any of them possess the methyl group at the 5-position, nor does Asano direct the person of skill to make any of these changes. (This was argued in the previous office action response which overcame the 103 rejection over Asano and Immune-strategy for compounds with the stereochemistry found in claim 65; these arguments are reproduced below for the sake of continuity.)

Asano: The elected compound of the instant application (wherein R is hydrogen) is shown below:



Asano does not disclose this compound, as the Examiner states. In Asano, none of compounds A_1, A_2, A_3, B_3, B_1, B_2 have an OH group at the 6-position; only C_1 shows an OH at this position. However, compound C_1 has an additional group (methyl) at the 5-position, as do four of the other six disclosed Asano compounds. The compound of Applicants' elected species does not contain this additional methyl group at this position. The stereochemistry of the elected compound, moreover, is different from that of either Asano compound (B_3 and C_1) having a C-7 hydroxyl. Lastly, no data or utility is disclosed for compound C_1, and compound B_3 (arguably the next closest compound to the elected species) shows the poorest inhibition of bacterial glucosidase of any of the tested compounds in the IC_{50} results given in Table 2. Thus, to get from Asano's compounds to the compound of Applicants' elected species, the person of skill would have to (1) choose the least potent species from Asano as the starting point [see Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007). "[T]he prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound."]; (2) remove a carbon substituent at C-5; (3) invert a hydroxyl at C-1; (4) invert a hydroxyl at C-7 and (5) invert a hydroxyl at C-6. The Examiner has provided no teaching that would motivate any of these changes. Whether or not Asano had taught the utility of his species as antibacterials (which he did not), a *prima facie* case of obviousness against the elected species could not exist.

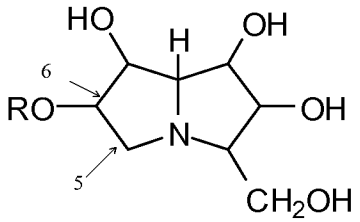
Immune-strategy: The Examiner contends that, "Immune-strategy teaches glycosidase inhibitor in combination with ZDV for the treatment of HIV. Treatment of HIV encompasses treatment of bacterial infections that result from the disease" (page 4, section 7 of Action). Applicants respectfully disagree that this reference is relevant to the claims of the instant application. Immune-strategy describes plans for using a combination therapy of a known antiretroviral (ZDV) and a glycosidase inhibitor for the treatment of HIV, a virus.

Any bacterial infection present in an HIV patient is merely a sequela of the viral infection, not the cause of it. The combination of ZDV and a glycosidase inhibitor will treat solely the viral cause, not the resulting bacterial infection. The combination of ZDV and a glycosidase inhibitor is not a known treatment for bacterial infection. Further, this is a combination therapy; there is absolutely no teaching that the glycosidase inhibitor by itself has any antibacterial activity whatsoever.

In the Immune-strategy reference, there is no action of a glycosidase inhibitor directly on bacterial cell walls. Indeed, there ARE no bacteria to act on, if the combination antiviral treatment has been effective. The prevention of the viral disease (HIV) prevents the occurrence of subsequent bacterial infection development. Claim 48 of the instant application specifically mentions the modification of bacterial cell walls ("A method according to claim 45 wherein the pyrrolizidine compound, when administered *in vivo*, modifies…bacterial cell walls"). This is clearly not the intention of the treatment in the Immune-strategy reference.

The person of skill would not have had any suggestion or motivation to combine Asano with Immune-strategy to arrive at the instant claims: Asano does not even disclose the instant species, and Immune-strategy discloses a treatment to a viral infection, not a modification of the bacterial wall. This would not have been obvious to try. The person of ordinary skill would not have had reason to attempt to combine these two references, nor would there have been a reasonable expectation of success. Applicants argue that this combination of references decidedly does not constitute a *prima facie* obviousness rejection. Withdrawal of this rejection is respectfully requested.

Since the rejection of the species was not supportable, the Examiner was required to continue examination of the remainder of the pending claims. Even when the entire claim set is considered, the above arguments overcoming Asano remain compelling. The broadest formula contained in the instant application is shown below:



Just as was found in the case of the elected species, this broader compound formula is not obvious in light of Asano. Asano clearly does not disclose the genus claimed nor any species within that genus. As discussed in the above arguments, the 5-position of Asano's Hyacinthacine C_1 contains a methyl group and doesn't disclose a utility. Those Asano compounds that have hydrogen at the 5-position (e.g. A_2) don't have the -OR group at the 6-position. Further, as mentioned above, the person of skill would still have to choose Asano's least potent species as the starting point, then change the structure by adding an -OR group and removing a methyl substituent. The *prima facie* obviousness rejection still cannot be made against the broad claims on the basis of the structures in the cited art.

However, in the interest of advancing prosecution, Applicants have amended the broadest independent claim (now claim 76) to illustrate specific stereochemistries of the compounds. Support for compounds with these stereochemistries can be found on pages 14-15, 39-40 and 43-44. The Asano compounds do not possess these stereochemistries. New claims 87 and 88 have also been added to cover compounds with stereochemistries other than those listed in claim 76; however, in these claims, R cannot be hydrogen. Even if the stereochemistry is the same as that found in the closest Asano compound, the person of skill would still not be motivated to add a methyl group and change the R group to arrive at the Asano compound. Based on these amendments, Applicants request the withdrawal of the 103(a) rejection.

Double Patenting

All pending claims have been rejected by the Examiner on the ground of nonstatutory obviousness-type double patenting as being unpatentable over copending applications 10/597,290 and 10/597,296. Applicants believe this rejection to be overcome based on the filing dates of the three applications:

Application No.	PCT Date	Earliest Priority Date
Instant	1/21/04	1/23/03
10/597,296	1/21/05	1/21/04
10/597,290	1/21/05	1/21/04.

As the two cited applications have not yet been issued, Applicants believe it to be unnecessary to file a terminal disclaimer in the instant application to overcome the double patenting rejection. Applicants respectfully request the withdrawal of this rejection.

Conclusion

Applicants respectfully assert that the amendments and arguments presented above overcome all rejections presented by the Examiner and believe the application is now in condition for allowance. The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to, Deposit Account No. 08-1935, Docket No. 3073.054.

Respectfully submitted,

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